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(54) Title: COMBINATION OF RENIN INHIBITOR AND DIURETICS

(57) Abstract: The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising (i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and (ii) the diuretic amiloride or triamterene or a pharmaceutically acceptable salt thereof, and (iii) a further diuretic (e.g. HCTZ) or a pharmaceutically acceptable salt thereof.

COMBINATION OF RENIN INHIBITOR AND DIURETICS

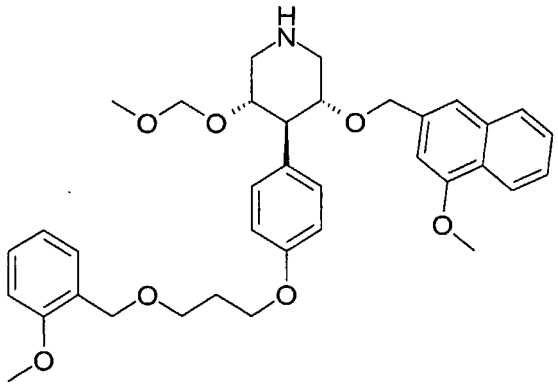
The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising

(i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ii) amiloride or triamterene or a pharmaceutically acceptable salt thereof and

(iii) a thiazide diuretic or a pharmaceutically acceptable salt thereof.

The class of renin inhibitors comprises compounds having differing structural features. For example, mention may be made of compounds which are selected from the group consisting of ditekiren (chemical name: [1S-[1R*,2R*,4R*(1R*,2R*)]]-1-[(1,1-dimethylethoxy)carbonyl]-L-proly l-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmrthyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-N-alfa-methyl-L-histidinamide); terlakiren (chemical name: [R-(R*,S*)]-N-(4-morpholinylcarbonyl)-L-phenylalanyl-N-[1-(cyclohexy lmethyl)-2-hydroxy-3-(1-methylethoxy)-3-oxopropyl]-S-methyl-L-cysteineamide); zankiren (chemical name: [1S-[1R*[R*(R*)],2S*,3R*]]-N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-m ethylhexyl]-alfa-[[2-[[(4-methyl-1-piperazinyl)sulfonyl]methyl]-1-oxo-3-phenylpropyl]amino]-4-thiazolepropanamide), especially the hydrochloride thereof; RO 66-1132 and RO-66-1168 of formulae



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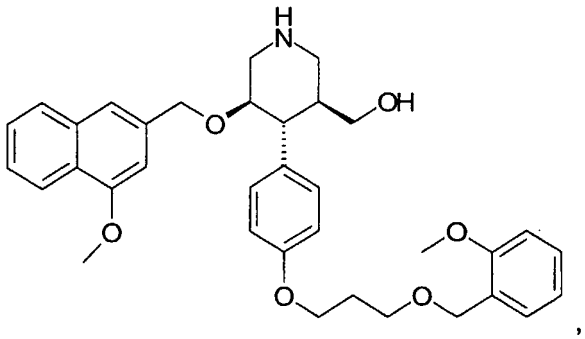
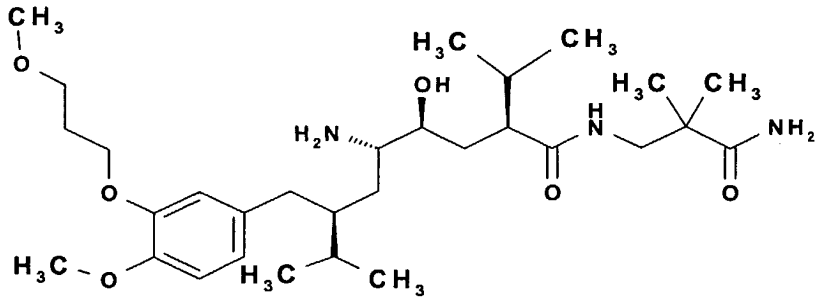


respectively.

Especially preferred is the compound of formula



(I),

chemically defined as 2(S),4(S),5(S),7(S)-N-(3-amino-2,2-dimethyl-3-oxopropyl)-2,7-di(1-methylethyl)-4-hydroxy-5-amino-8-[4-methoxy-3-(3-methoxy-propoxy)phenyl]-octanamide (generic name: aliskiren), specifically disclosed in EP 678503 A, or a pharmaceutically acceptable salt, especially the hemi-fumarate, thereof.

A preferred pharmaceutically acceptable salt of amiloride is the hydrochloride.

A thiazide diuretic is, for example, selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorthalidone. Most preferred is hydrochlorothiazide.

Preferred are combinations, such as combined preparations or pharmaceutical compositions, respectively, comprising

(i) a renin inhibitor or a pharmaceutically accepted salt thereof and
(ii) amiloride or a pharmaceutically acceptable salt thereof and
(iii) hydrochlorothiazide or a pharmaceutically acceptable salt thereof.

Most preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising

(i) aliskiren or a pharmaceutically accepted salt thereof; and
(ii) amiloride hydrochloride; and
(iii) hydrochlorothiazide.

The structure of the active agents identified by generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Life Cycle Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture

and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

The diuretics amiloride or triamterene or, in each case, a pharmaceutically acceptable salt thereof inhibit the Na+ channels in the distal tubules and collecting ducts by increasing the loss of sodium and chloride ions while reducing the excretion of potassium. It is known that the thiazide diuretics reduce the re-absorption of electrolytes from renal tubules, thereby increasing the excretion of sodium and chloride ions and consequently of water. The excretion of potassium is also increased by administering e.g. hydrochlorothiazide. The combination of amiloride, especially the hydrochloride thereof, or triamterene, respectively, and a thiazide diuretic, for example, hydrochlorothiazide, increases the excretion of sodium and chloride ions while diminishing the kaliuretic effects.

All the more surprising is the experimental finding that the combined administration of the combination of

(i) a renin inhibitor a pharmaceutically acceptable salt thereof, and

(ii) amiloride or triamterene or a pharmaceutically acceptable salt thereof and

(iii) a further diuretic or a pharmaceutically acceptable salt results not only in a beneficial, especially potentiation, preferably a synergistic, therapeutic effect, but also in additional benefits resulting from the combined treatment and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

In particular, all the more surprising is the experimental finding that the combination of the present invention results not only in a beneficial, especially a potentiation, preferably synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions as specified hereinafter.

Furthermore, a surprising effect of the combination of the present invention is the fact that a higher blood pressure lowering with lower dose of every component of the triple therapy.
- Better potassium handling and homeostasis.
- Better protection of the myocardium because of the haemodynamic effects of the three components and the protective effect of aliskiren and amiloride or triamterene, respectively. In fact, aliskiren by inhibiting renin protects against the detrimental actions of myocardial ischemia on myocardial perfusion and remodeling and amiloride or triamterene, respectively, by blocking Na+/H+ exchanger that play a role in ischemia-reperfusion injury protects the myocardium to a high extent in repetitive ischemia and acute myocardial infarction.

It can be shown by established test models and especially those test models described herein that the combination of the therapeutic agents selected from the group consisting of (i) to (iii) results in a more effective prevention or preferably treatment of diseases specified in the following.

If taken simultaneously, this results not only in a further enhanced beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the simultaneous treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with diabetes mellitus, for a number of combinations as described herein. Moreover, for a human patient, especially for elderly people, it is more convenient and easier to remember to take three tablets at the same time, e.g. before a meal, than staggered in time, i.e. according to a more complicated treatment schedule. More preferably, all three active ingredients are administered as a fixed combination, i.e. as a single tablet, in all cases described herein. Taking a single tablet is even easier to handle than taking three tablets at the same time. Furthermore, the packaging can be accomplished with less effort.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of the present invention is greater than the sum of the effects that result from methods and compositions comprising the active ingredients of this invention separately.

The person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the class of AT_1-receptor antagonists or diuretics, respectively, or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The beneficial effects on blood pressure can, for example, be demonstrated in the test model as disclosed in R.L. Webb et al., in J. Hypertension, 16:843-852, 1998.
Methods:
The combination according to the present invention comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered by various routes of administration but are tested in this example using a continuous infusion via subcutaneously-implanted osmotic minipumps. Each agent can be tested over a wide-range of dosages to determine the optimal drug level for each agent in combination to elicit the maximal response. For these studies, it is preferred to use treatment groups consisting of at least 6 animals per group. Each study is best performed in which the effects of the combination treatment group are determined at the same time as the individual components are evaluated. Although drug effects may be observed with acute administration (such as 1 day), it is preferable to observe responses in a chronic setting as shown below in which experiments were done over a two to three week observation period. The long-term study is of sufficient duration to allow for the full development of compensatory responses to occur and therefore, the observed effect will most likely depict the actual responses of the test system representing sustained or persistent effects. The effects on blood pressure depicted below represent a synergistic antihypertensive effect when the three agents are used in combination.

Statistical Analysis:

The combination therapy can be compared to that of the monotherapy groups by determining the maximum change in blood pressure or the area under the curve (AUC) for change in blood pressure over time in each of the treatment groups. All values are represented as the group mean $\pm$ SEM. Statistical significance is obtained when $p < 0.05$. The AUC values for each of the treatment groups can be compared statistically using a one-way ANOVA followed by the appropriate post-hoc analysis, for example by performing a Tukey's test.

Results:

Blood pressure can be reduced to a similar degree using lower dosages of each of the components when given in combination than when the individual monotherapies are administered. An additional unexpected finding is that the blood pressure can be lowered to a greater extent with the combination than when the individual compound of formula (I) or a pharmaceutically acceptable salt thereof is given alone at a higher dosage.

The beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardiovasc. Pharmacol. 27:347-354, 1996.

For example, the valuable potential of the combination of the present invention for the prevention and treatment of myocardial infarction (including the post-myocardial infarction indication to delay the progression to congestive heart failure) can be found using the following test model.

Study design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats (normal Sprague Dawley rat or Dahl salt-sensitive rat on a high salt diet) is used as a model of acute myocardial infarction in a normotensive or hypertensive animal, respectively. The experiments are carried out with 5 treatment groups characterized by following features:

- sham-operated animals
- CAO + vehicle
- CAO + aliskiren (al) or a pharmaceutically acceptable salt, thereof,
- CAO + amiloride (ami),
- CAO + hydrochlorothiazide (HCTZ);

• CAO + aliskiren or a pharmaceutically acceptable salt thereof, + amiloride + hydrochlorothiazide.

During the study following variables are measured:
• infarct size
• LV chamber volume
• interstitial and perivascular collagen density in spared LV myocardium
• COL-I and COL-III protein content in spared LV myocardium by Western blot
• cardiomyocytes cross-sectional area and length in sections of LV myocardium
• plasma concentrations of renin and aldosterone
• urine concentration of sodium, potassium and aldosterone
• blood pressure in conscious animals
• LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct size: Six µm-thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and the image acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a software specifically developed (Porzio *et al.,* 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.,* 1995).

Histology: Hearts are fixed *in situ*, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.,* 1998).

Collagen content in LV spared myocardium: LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electro-blotted onto

nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for colagen type I) or peroxidase (collagen type III).

Left ventricular chamber volume: LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.,* 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left ventricular hemodynamics: A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time (+dP/dt) and heart rate.

Non-invasive blood pressure: Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine electrolytes, hormones: Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C_{18} columns (Varian), separated by HPLC (Apex-II C18, 3 µm, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein *et al.,* 1981). Plasma and urine aldosterone, and plasma angiotensin II are determined with specific radioimmunoassays (Aldoctk-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flame photometry.

Sample size

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidizing agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial disfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGFb, PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelial dysfunction can be demonstrated in the following pharmacological test:

Material and methods
Male 20-24 week-old SHR, purchased from RCC Ldt (Fullingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag 9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7).

The rats can be divided into 5 groups: group 1, control (n = 40); Group 2, aliskiren (al; n = 40); Group 3, amiloride (ami; n = 30); Group 4, hydrochlorothiazide (HCTZ; n = 30); Group 4, a combination (al-ami-HCTZ) (n = 30). The drugs are administered either in drinking fluid or admixed with food. The doses to be used are selected from the work of Sweet et al. (1987) indicating significantly increased survival in rats with healed myocardial infarction. The pressor effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reducted

after treatment with the compound of formula (I) in form of the hemi-fumarate (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na^+ and K^+ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical analysis:

All data are expressed as mean ± SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, for comparison between the different groups. Differences with a probability value of less than 0.05 are deemed statistically significant.

Results:

Even at non-blood pressure-reducing doses, administration of the combination of the present invention leads to significant improvements in survival rates.

An improvement of regression of artherosclerosis without affecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the compounds or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test

model described, e.g., by MV McConnell et al. Arterioscler Thromb Vasc Biol. 1999;19:1956-9.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Design of Clinical Programs

A factorial design study in naïve or previously treated hypertensive patients is initiated in order to select the more appropriate dose(s) for subsequent use. The positive outcome of the selected dosage is based on synergy in blood pressure lowering, low incidence of side effects and better potassium handling of the combination. This study includes up to 120 patients in every cell of the explored doses of monotherapy and/or marketed combination of two of the three components of the triple combination.

Furthermore, non-responder study is carried out to show that the add on of a third agent of the combination may bring additional blood pressure lowering and more patients under control without increasing the side effects.

These study(s) show that this triple combination provides additional myocardial protection in patients having myocardial infarction, acute coronary syndrome, ischemic heart disease, myocardial revascularization at the acute or chronic phase of coronary occlusion. This claim is supported by clinical studies measuring markers of myocardial ischemia and injury such as troponin T and I, CPK MB, myoglobin, as well as, markers of myocardial function such as ejection fraction, left ventricular dimensions and contractility measured by MRI, echography, scintigraphy etc. In addition measurement of myocardial salvage by technetium scintigraphy or other appropriate measure of myocardial salvage.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

Accordingly, the invention furthermore relates to a method for the prevention of, delay of progression of, treatment of at least one disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia,

(e) glaucoma;

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a combination of

(i) the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent comprising

(ii) amiloride or triamterene or a pharmaceutically acceptable salt thereof and

(iii) a further diuretic (e.g. HCTZ) or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention relates to the use of a combination comprising

((i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ii) amiloride or triamterene or a pharmaceutically acceptable salt thereof and

(iii) a further diuretic (e.g. HCTZ) or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of at least one disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
(c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;
(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia;
(e) glaucoma;
(f) isolated systolic hypertension (ISH),
(g) diabetic retinopathy, and
(h) peripheral vascular disease.

The invention furthermore relates to a pharmaceutical composition for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of
(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
(c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;
(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia;
(e) glaucoma;
(f) isolated systolic hypertension (ISH),
(g) diabetic retinopathy, and
(h) peripheral vascular disease;
comprising
((i) a renin inhibitor a pharmaceutically acceptable salt thereof, and

(ii) amiloride or triamterene or a pharmaceutically acceptable salt thereof and
(iii) a further diuretic (e.g. HCTZ) or a pharmaceutically acceptable salt thereof;
and a pharmaceutically acceptable carrier.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

A further aspect of the present invention is a kit for the prevention of, delay of progression of, treatment of a disease or condition according to the present invention comprising
(a) an amount of aliskiren or a pharmaceutically acceptable salt thereof in a first unit dosage form;
(b) an amount of therapeutic agents (ii) and (iii), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
(c) a container for containing said first, second etc. unit forms.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or

condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

The pharmaceutical preparation will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet for oral treatment.

Aliskiren, as a representative of the class of renin inhibitors, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 10 to about 1500 mg, of aliskiren which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of aliskiren. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

Hydrochlorothiazide will be supplied in of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 5 mg to about 50 mg which may be applied to patients. Preferred doses per unit dosage form is 6,25 mg, 12,5 mg or 25 mg. The application of the active ingredient may occur up to three times a day.

The dosage of amiloride or triamterene, respectively, are those that are normally being used for mono-therapy, most preferably, the lower range of the prescribed doses. The application of the active ingredient may occur up to three times a day.

Especially preferred are low dose combinations.

What is claimed is

1. A combination, such as a combined preparation or pharmaceutical composition, respectively, comprising

(i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ii) the diuretic amiloride or triamterene or a pharmaceutically acceptable salt thereof, and

(iii) a further diuretic or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1, comprising

(i) aliskiren or a pharmaceutically accepted salt thereof and

(ii) amiloride or a pharmaceutically acceptable salt thereof and

(iii) hydrochlorothiazide or a pharmaceutically acceptable salt thereof.

3. A combination according to claim 1, comprising

(i) aliskiren hemi-fumarate and

(ii) amiloride hydrochloride and

(iii) hydrochlorothiazide.

4. A pharmaceutical composition comprising a combination according to any one of claims 1 to 3.

5. A pharmaceutical composition for the prevention of, delay of progression of, treatment of at least one disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia,

(e) glaucoma;

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising

(i) a renin inhibitor or pharmaceutically acceptable salt thereof, and

(ii) the diuretic amiloride or triamterene or a pharmaceutically acceptable salt thereof, and

(iii) a further diuretic or a pharmaceutically acceptable salt thereof; and

(iv) an auxiliary.

6. Use of a combination comprising

(i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ii) the diuretic amiloride or triamterene or a pharmaceutically acceptable salt thereof, and

(iii) a further diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, treatment of at least one disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia,

(e) glaucoma;

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease.

7. A method for the prevention of, delay of progression of, treatment of at least one disease or condition selected from the group consisting of

(a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

(b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;

(c) endothelial dysfunction with or without hypertension,

(d) hyperlipidemia, hyperlipoproteinemia, and hypercholesterolemia,

(e) glaucoma;

(f) isolated systolic hypertension (ISH),

(g) diabetic retinopathy, and

(h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof jointly therapeutically effective amounts of

(i) a renin inhibitor or a pharmaceutically acceptable salt thereof, and

(ii) the diuretic amiloride or triamterene or a pharmaceutically acceptable salt thereof, and

(iii) a further diuretic (e.g. HCTZ) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/EP2005/001580

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P9/00 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MAIBAUM J ET AL: "Renin inhibitors as novel treatments for cardiovascular disease" EXPERT OPINION ON THERAPEUTIC PATENTS 01 MAY 2003 UNITED KINGDOM, vol. 13, no. 5, 1 May 2003 (2003-05-01), pages 589-603, XP002327881 ISSN: 1354-3776 page 598, left-hand column, paragraph 3 - page 599, left-hand column, paragraph 2 ----- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 2005	25/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Escolar Blasco, P

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Internat plication No
PCT/EP2005/001580

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1987, LUMME J A J ET AL: "Combined action of enalapril or timolol with hydrochlorothiazide plus amiloride in hypertension" XP002327884 Database accession no. EMB-1988051855 abstract & ANNALS OF CLINICAL RESEARCH 1987 FINLAND, vol. 19, no. 5, 1987, pages 344-350, ISSN: 0003-4762	1-7
A	BROWN M J ET AL: "Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT)." LANCET. 29 JUL 2000, vol. 356, no. 9227, 29 July 2000 (2000-07-29), pages 366-372, XP002327882 ISSN: 0140-6736 abstract	1-7
Y	WO 03/097098 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; FELDMAN, DAVID, LOUIS; WEBB, RANDY,) 27 November 2003 (2003-11-27) page 5, line 1 - page 6, last line	1-7
Y	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1984, ALON U ET AL: "Additive hypocalciuric effects of amiloride and hydrochlorothiazide in patients treated with calcitriol" XP002327885 Database accession no. EMB-1985000851 abstract & MINERAL AND ELECTROLYTE METABOLISM 1984 SWITZERLAND, vol. 10, no. 6, 1984, pages 379-386, -/--	1-7

INTERNATIONAL SEARCH REPORT

Internat plication No
PCT/EP2005/001580

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HIMMELMANN ANDERS ET AL: "Remikiren (RO 42-5892): An orally active renin inhibitor in essential hypertension: Effects on blood pressure and the renin-angiotensin-aldosterone system" AMERICAN JOURNAL OF HYPERTENSION, vol. 9, no. 6, 1996, pages 517-522, XP002327883 ISSN: 0895-7061 abstract	1,4-7
A	US 5 047 235 A (LOSSNITZER ET AL) 10 September 1991 (1991-09-10) column 2, lines 4-50	1,4-7

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/001580

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 7: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/001580

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